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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,134	07/02/2002	Raghuveer Basude	D2027/20139	8214

3000 7590 06/14/2007

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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
06/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,134	BASUDE, RAGHUVEER ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/07 has been entered.

Status of Claims

Claims 1-16 are pending in the application.

Claims 15-16 are new.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Rasor et al. US 5141738 (hereinafter "Rasor").

Rasor discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (col. 8, lines 24-26) and a gas microbubble, (col. 6, lines 3-11). The gas microbubble attaches or in contact with the microparticle, (column 6, line 57). The compositions are prepared by methods including storing the microparticle in a

gaseous environment and introducing the microparticles into a liquid, (col. 9 bridging to 10 and examples). Also, since the microparticle contains a lipophilic surface, it would have affinity for lipophilic gases such as perfluorocarbons that are somewhat lipophilic by nature. In addition, the step of forming the gas microbubble recited in claim 1 and 2 of the current application is considered a product by process limitation, wherein only a specific single step excludes adding surfactant, this limitation does not exclude surfactant in the microbubble and consequently does not differentiate over the prior art. Rasor also teaches that the ultrasonic diagnostics comprising a liquid vehicle containing (a) suspended therein microparticles of a mixture of at least one C_8 -C_{20} fatty acid and at least one solid that is not a surfactant and (b) microbubbles (abstract), the disclosure does not include the surfactant and is administered intravenously (into the blood).

Claims 1-7 and 9-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Schneider US 5,271,928 (hereinafter "Schneider").

Schneider discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a liposome) and microbubbles, which

are associated therewith, in that the liposomes stabilize the microbubbles, see (col. 4, lines 6-36). The compositions are prepared by a method of storing the liposomes in a gaseous environment and introducing the liposomes into a liquid, (col. 4, lines 37-55). The compositions may further include drugs, such as radionuclide for nuclear medicine, (col. 10, lines 3-5) as well as, a targeting moiety, (column 9, lines 36-66). Also, since the microparticle contains a lipophilic surface, it would have affinity for

lipophilic gases such as perfluorocafbons that are somewhat lipophilic by nature. Schneider also disclosed that his composition is suitable for injection into the bloodstream and body cavities of living beings, comprising a suspension of stabilized air or gas microbubbles in a physiologically acceptable aqueous carrier (claim 1).

Note that amending claim 1 by adding optionally a targeting moiety and a drug would not change the status of the rejection.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasor 5141738 or Schneider US 5271928 in view of Unger US 5542935 (hereinafter "Unger").

Rasor and Schneider disclose compositions comprising a microparticle and microbubble for methods of ultrasound and/or drug delivery, as discussed above.

Rasor and Schneider fail to disclose that the methods of drug delivery include a step of insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Unger discloses compositions comprising microbubbles that are useful for both ultrasound imaging and drug delivery, see abstract and column 35, lines 4-5. Unger teaches that the microbubbles may further comprise various drugs that are released by

insonation to provide the advantage of site-specific delivery to a desired site, (e.g., the drug is not released until the particles reach the treatment site), (col. 35, lines 29+). Unger also disclosed that the microsphere might be made of starch. This disclosure reads on the requirement of new claim 15 (col. 29, lines 12+), and that the microspheres are preferably sufficiently stable in the vasculature such that they withstand recirculation. The gaseous precursor-filled microspheres may be coated such that uptake by the reticuloendothelial system is minimized. Useful coatings include, for example, polyvinyl alcohol, and starch (col. 19, lines 40+ and).

It would have been obvious to one of ordinary skill in the art to use the compositions disclosed by Rasor or Schneider for drug delivery by insonating the microbubbles at a desired site in vivo because Unger teaches that analogous gas-filled microbubbles may further contain various drugs to yield a drug delivery means having the advantage of site-specific delivery by insonating the microbubbles at a desired site in vivo. One of ordinary skill in the art would have been motivated to employ the drug delivery methods and the materials that form the microspheres disclosed by Unger using the compositions disclosed by Rasor and Schneider to obtain a composition which is useful for both ultrasound imaging and site-specific therapy using a single administration, wherein the insonating step provides release of the drug specifically at the treatment site.

Response to Arguments

3. Applicant's arguments filed 3/26/07 have been fully considered but they are not persuasive.

- Applicant asserts that, gas microbubbles are formed by introducing a gas into water, a buffer, or blood without surfactant. This contradicts with the anticipation of instant claims 1, and 10 and dependent claims by Rasor and Schneider. Applicant also argues that since the two references do not anticipate, Unger would not remedy the deficiency because a prima facie case of obviousness was not accomplished.

In response to these arguments: it is the position of the examiner that since a surfactant is often an integral part of a gas microbubble, as shown by both Rasor and Schneider, the term "microbubble" cannot be used to exclude surfactant. Therefore, the term "a gas microbubble formed by a introducing a gas into...." does not exclude surfactant, as asserted. Further, the support for the amendment cited by the applicant demonstrates clearly that when dry relatively hydrophobic microparticle from a gaseous environment is introduced into a liquid such as buffer, water or blood, the particles carries with it some of the gas into the liquid, which indicates that introducing the gas in the liquid medium is associated with the microparticle, which in turn makes it unclear how this would exclude surfactant from either the microparticles or gas microbubble or just from gas microbubble, as appears to be amended. Further, note in columns 5-6 of Rasor, that the microbubble are formed by dispersion in water and therefore it is the microparticles which stabilize the gas bubbles of Rasor that contain the surfactant and not the gas microbubbles themselves. Rasor also discloses that his composition is administered intravenously (see abstract), which reads on the limitations amended in the claim. Finally, the phrase "consisting essentially" would not exclude coating or adding a surfactant because the claims are not limited to exclusion of a surfactant in

making the claimed microbubbles. This assertion appears to contradict the definition of gas microbubble as known in the art. In addition, the assertion appears to contradict the actual invention, which uses a surfactant in the microparticles that stabilize the gas microbubbles. The term "consisting essentially o" in the preamble of the claim cannot be used to specifically exclude something from one component in a claim while allowing it in another (i.e., excluding from the gas microbubbles but not the microparticles that stabilize the microbubbles). Further, the surfactants used in Schneider are used in the liposomes which are used to stabilize the gas bubbles that do not contain surfactant, which is the same as is asserted is being claimed. It is also noted that some of the dependent claims are product-by process claims, which are examined as reading on the product. Also, the process in these claims is open-ended which recite comprising in the listed steps. Schneider also discloses that his invention composition suitable for injection into the bloodstream and body cavities of living beings, comprising a suspension of stabilized air or gas microbubbles in a physiologically acceptable aqueous carrier (claim 1), this aqueous carrier may be water, buffer, or blood.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nabila Ebrahim
6/4/07

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER